REMARKS

Claims 17-32 are currently pending in this application. Claims 17, 21-23, 25, 27 and 29-32 have been withdrawn from further consideration as being drawn to non-elected subject matter. Claims 18-20, 24, 26, 28 and 32 have been rejected. Specifically, claim 28 stands rejected under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 103. Applicants respectfully request reconsideration and withdrawal of these rejections for the reasons stated below.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

Claim 28 has been rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification with regard to a method of preventing vaginal dryness. Applicants have amended claim 28 to replace "preventing" with "reducing a risk of developing". Support for this amendment can be found, for example, on page 3, lines 8-15 of the specification. In view of this amendment, Applicants respectfully request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Claims 18, 19, 24, 26, 28 and 32 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kragie[1] in view of Willhite[2]. Claim 20 has been rejected under 35 U.S.C. § 103(a) unpatentable over Kragie in view of Willhite and Younglai[3]. Claims 18, 19, 24, 26, 28 and 32 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Sitruk-Ware[4] in view of Spicer[5] and Willhite. Claims 20 has also been rejected under 35 U.S.C. § 103(a) as unpatentable over Sitruk-Ware in view of Willhite and Younglai. Applicants respectfully traverse these rejections because there was no reasonable expectation

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[1] United States Published Patent Application Number 2004/0192598 to Kragie ("Kragie").

[2] Willhite *et al.*, "Urogenital Atrophy: Prevention and Treatment," PHARMACOTHERAPY (2001) 21(4): 464-480 ("Willhite").

[3] Sitruk-Ware *et al.*, "Local hormonal treatment for urogenital atrophy after menopause," Schweiz. Rundsch., Med. Praxis (1997) 86(33): 1245-1248 ("Sitruk-Ware").

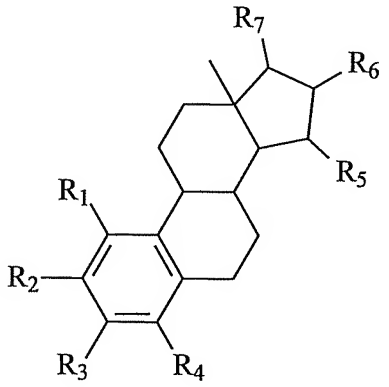
[4] Sitruk-Ware *et al.*, "Local hormonal treatment for urogenital atrophy after menopause," Schweiz. Rundsch., Med. Praxis (1997) 86(33): 1245-1248 ("Sitruk-Ware").

[5] United States Patent Number 5,21,952 to Spicer ("Spicer").

in the art that the recited estrogenic component would be pharmacologically useful, and because it was unexpected to discover that the recited estrogenic component is pharmacologically useful.

I. THE CLAIMED INVENTION

The invention as recited in claims 28 is directed to a method of treating or preventing vaginal dryness comprising applying to a composition. The composition contains at least 5 μg/g of an estrogenic component. The estrogenic component is selected from the group consisting of substances represented by the following formula:



in which formula R_1, R_2, R_3, R_4, independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms; each of R_5, R_6, R_7 is a hydroxyl group; no more than 3 of R_1, R_2, R_3, R_4 are hydrogen atoms; precursors capable of liberating a substance according to the aforementioned formula when used in the present method; and mixtures thereof. In one embodiment, the estrogenic component is estetrol. The composition also contains a cosmetically acceptable vehicle. Claims 18, 19, 20, 24 and 26 depend from claim 28.

II. THE CITED REFERENCES

The Patent Office contends that Kragie teaches using estrogen function replacement agent(s) to treat vaginal atropy, and that Willhite teaches that vaginal atropy is synomous with vaginal dryness.[6] Kragie is directed to compositions and methods to replace estrogen in humans and other animals.[7] It describes a method for alleviating adverse side

[6] Office Action at pages 10-11.

[7] Kragie at abstract.

effects and/or enhancing the beneficial efficacy of an aromatase inhibitor in a subject by administering a combination of an aromatase inhibitor and an estrogen function replacement (EFR) agent. An EFR agent "is defined as one that can selectively, totally, or partially replace the function performed by the estrogen compounds that are usually synthesized by the aromatase enzyme."[8] Kragie provides an overly broad list of EFR agents, which include: estradiol, ethinyl estradiol, estradiol valerate, estradiocypionate, estrone, estriol, estetrol, estropipate, 2-methoxyestradiol, hydroxyestrones, sodium estrone sulfate, equine estrogens, equilenin, equilin, conjugated estrogens, esterified estrogens, micronized estrogens, synthetic estrogens, nonsteroidal estrogens; phytoestrogens such as isoflavonoids, flavonoids, lignans, coumestan, and other natural compounds derived from plants such as soya, tea, fruits and vegetables; synthetic phytoestrogen ipriflavone; genistein, daidzein, enterolactone; selective estrogen receptors ligands and modulators factors (such as raloxifene, tamoxifen, indenoindoles, and estrogen partial agonist/antagonists); catechol estrogens and their metabolites (such as 2-hydroxyestrone, 2-hydroxyestradiol and their 4-hydroxy isomers); 2,3-estrogen o-quinone, diethylstilbestrol, nitro-estrogens, catechol estrogen 3,4-quinone, estrophilin, formatrix, methallenestril, quinestrol, chlorotrianisene, norethisterone, norethindrone, 17-alpha-ethynyl-19-nortestosterone; dienestrol, norethynodrel, promethestrol, mestranol, tamoxifen, hydroxytamoxifen, clomiphene, chlorotrianisene, nafoxidine, hexestrol, niifepristone, RU 486; bisphenol A, p-tert-octylphenol and other endocrine disruptors; B-ring homologated estradiol analogues; estrogen receptor elements (such as estrogen receptor activation factor, activated estrogen receptor complex, and Heat Shock Protein).[9] However, at the relevant time, one of ordinary skill in the art would not have picked estetrol from this long list, or even considered using estetrol when the relevant scientific literature taught that estetrol was believed not to be pharmacologically useful.

Kragie discusses different modes of administration. The method comprises administering EFR agent(s) through oral, inhaled, topical, parenteral, rectal, intravaginal, intraurethra, intrathecal or implanted route(s) in combination with the exposure to aromatase inhibitor(s).[10] However, Kragie notes that EFR agents are currently used in perimenopausal

[8] Kragie at ¶ 13.

[9] Kragie at ¶¶ 38 and 39.

[10] Kragie at ¶ 14.

and menopausal women.[11] Spefically, Kragie states that "... EFR agents are currently used in perimenopausal and menopausal women to prevent and/or treat vaginal atrophy, hypogonadism, diminished libido and to relieve vasomotor symptoms, urogenital atrophy, osteoporosis, alopecia and other symptoms and signs associated with menopause."[12]

The Office Action cites Willhite as demonstrating "[t]hat urogenital atrophy is also known as vaginal dryness."[13]

The Office Action cites Younglai as teaching "estetrol (i.e. E4) has many precursors (see pg. 1617, figure 2). In fact, Younglai et al. teach 15-α-hydroxyandrostenedione or dehydroxyandrostenedione as precursors of E4 and containing acyl moiety group (instant claim 20)."[14]

The Patent Office also contends that the combination of Sitruk-Ware, Spicer and Willhite likewise suggest the recite invention.[15] The Patent Office contends that Sitruk-Ware teaches that estrogenic treatment is an efficient way to correct vaginal dryness.[16] Sitruk-Ware specifically teaches that "[t]he post-menopausal urogenital symptoms connected with low estrogen level are manifested several years of hormonal deficit and are generally frequent in untreated elderly women. Estrogenic therapeutics, which are administered systemically or genitally, for the most part are capable of rapidly correcting or at least ameliorating the symptoms."[17] It further states that "[p]ost-menopausal low estrogen level will, in the medium term, be manifested at the urogenital level by irritation and vaginal dryness, ..."[18] Although it states that "[a]ny systemic estrogenic therapeutic is, of course, understood as being capable of correcting urogenital symptoms, ..."[19], Sitruk-Ware only discusses the following estrogens: estriol, promestriene, estradiol, estrone – conjugated

[11] Kragie at ¶ 73.

[12] Kragie at ¶ 73.

[13] Office Action at page 12.

[14] Office Action at page 13.

[15] Office Action at pages 14-16.

[16] Office Action at page 14.

[17] Sitruk-Ware at page 2, lines 2-7.

[18] Sitruk-Ware at page 3, lines 15-18.

[19] Sitruk-Ware at page 4, lines 7-9.

estrones.[20] The Patent Office acknowledges that Sitruk-Ware does not address the use of estetrol.[21]

To address this short-coming, the Patent Office contends that Spicer teaches the that estetrol may be employed in composition formulated for vaginal delivery.[22] Spicer describes a method for inhibiting conception in mammals, especially human females, and to formulations for use in such methods.[23] Specifically, Spicer states that:

> in accordance with the present invention there is provided a contraceptive delivery system and method for preventing pregnancy in a mammal (in particular, a human female) which comprises administering over an extended period of time (on the order of about 2 to about 6 months) an amount of a GnRH composition effective to suppress LH and FSH (with resultant inhibition of ovulation and ovarian sex-steroid production); an amount of an estrogenic steroid effective to counteract the possibility of side effects which may develop during prolonged therapy with GnRH, including but not limited to: symptoms of the menopause, vasomotor instability, loss of bone mineral content, rise in serum total or low-density cholesterol or its fractions, and urogenital atrophy; together with a short-term administration (on the order of about 5 to 20 days, preferably 10 to 15 days) of an amount of progestational steroid effective to counteract the possibility of endometrial hyperstimulation, hyperplasia or carcinoma which may develop during prolonged therapy with estrogenic steroids.[24]

Like Kragie, Spicer also provides an overly broad list of estrogens. Specifically, Spicer states that

> [n]atural and synthetic estrogenic compositions which can be used according to the invention described herein include natural estrogenic hormones and congeners, including but not limited to estradiol, estradiol benzoate, estradiol cypionate, estradiol valerate, estrone, diethylstilbestrol, piperazine estrone sulfate, ethinyl estradiol, mestranol, polyestradiol phosphate, estriol, estriol hemisuccinate, quinestrol, estropipate, pinestrol and estrone potassium sulfate. Equine estrogens, such as equilelinin, equilelinin sulfate and estetrol, may also be employed.[25]

However, there is no reason why one would pick estetrol from this long list where estetrol is listed as a mere possibility rather than part of the invention, or would consider using estetrol

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[20] Sitruk-Ware at pages 4-10.

[21] Office Action at page 14.
[22] Office Action at page 15.

[23] Spicer at column 1, lines 6-8.
[24] Spicer at column 3, lines 32-52.
[25] Spicer at column 5, lines 50-61.

when the relevant scientific literature taught that estetrol was believed not to be pharmacologically useful.

Point I. There was no reasonable expectation that estetrol would be pharmacologically useful.

None of these references establish that the recited estrogenic component is pharmacologically useful. Without such a disclosure, one of ordinary skill in the art would not reasonably expect estetrol to be useful in the recited method because, based on the scientific data published prior to the publication of this invention, such a person expected estetrol not to be pharmacologically useful.

Prior to the disclosure of the present invention, estetrol was believed to be a very weak natural estrogen.[26] In fact, a person of ordinary skill in the art believed that estetrol would not have any meaningful pharmacological effect due to its low estrogenic potency, and the fact that one would have expected estetrol to be similar to the natural estrogens estradiol and estriol in exhibiting a very short elimination half-life. The specification identifies several references that establish estetrol's low receptor binding affinity and poor estrogenicity:

- Levine et al., 1984. Uterine vascular effects of estetrol in non-pregnant ewes. Am. J. Obstet. Gynecol., 148:73, 735-738: "When intravenously administered in non-pregnant ewes, estetrol is 15 to 30 times less potent than estriol and 17.beta.-estradiol in uterine vasodilation".
- Jozan et al., 1981. Different effects of oestradiol, oestriol, oestetrol and of oestrone on human breast cancer cells (MCF-7) in long term tissue culture. Acta Endocrinologica, 98, 73-80: "Estetrol agonistic potency is 2% of the magnitude observed for 17β-estradiol in in-vitro cell proliferation".
- Holinka et al., 1980. Comparison of effects of estetrol and tamoxifen with those of estriol and estradiol on the immature rat uterus. Biol. Reprod. 22, 913-926: "Subcutaneously administered estetrol has very weak uterotrophic activity and is considerable less potent than 17β-estradiol and estriol".
- Holinka et al., 1979. In vivo effects of estetrol on the immature rat uterus. Biol. Reprod. 20, 242-246: "Subcutaneously administered estetrol has very weak uterotrophic activity and is considerable less potent than 17β-estradiol and estriol".
- Tseng et al., 1978. Heterogeneity of saturable estradiol binding sites in nuclei of human endometrium. Estetrol studies. J. Steroid Biochem. 9, 1145-1148:

[26] See Holinka (1980), *infra* at abstract.

"Relative binding of estetrol to estrogen receptors in the human endometrium is 1.5% of 17β-estradiol".

- Martucci et al., 1977. Direction of estradiol metabolism as a control of its hormonal action-uterotrophic activity of estradiol metabolites. Endocrin. 101, 1709-1715: "Continuous administration of estetrol from a subcutaneous depot shows very weak uterotrophic activity and is considerably less potent than 17.beta.-estradiol and estriol".
- Tseng et al., 1976. Competition of estetrol and ethynylestradiol with estradiol for nuclear binding in human endometrium. J. Steroid Biochem. 7, 817-822: "The relative binding constant of estetrol binding to the estrogen receptor in the human endometrium is 6.25% compared to 17β-estradiol (100%)".
- Martucci et al., 1976. Uterine estrogen receptor binding of catecholestrogens and of estetrol (1,3,5(10)-estratriene-3,15alpha,16alph, 17beta-tetrol). Steroids, 27, 325-333: "Relative binding affinity of estetrol to rat uterine cytosol estrogen receptor is 0.5% of 17β-estradiol (100%). Furthermore, the relative binding affinity of estetrol to rat uterine nuclear estrogen receptor is 0.3% of 17β-estradiol (100%)".[27]

To further evidence these points, Applicants submit declarations from third-party artisans in the field, and a declaration from one of the co-inventors. As these declarations establish, prior to the publication of this invention, one of ordinary skill in the art believed that estetrol would not have been pharmacologically useful.[28] This is because it was known in the art that estetrol had a substantially lower receptor affinity than estradiol or estriol.[29] Specifically, one of ordinary skill would have expected estetrol to be less effective than estradiol or estriol because Holinka (1980) suggests that estetrol is a much weaker estrogen than the already weak estrogen estriol, given that estetrol injected subcutaneous at 50 μg/100 g body mass exhibited less estrogenic activity than estriol injected subcutaneous at 1 μg/100 g body mass.[30] Estriol is a very weak estrogen due to its low receptor affinity in combination with its very short half-life of 5-10 minutes.[31] Holinka (1980) teaches that estrogenic activity of estetrol is at least 50 times lower than that of a weak estrogen for which

[27] Specification at pages 4-5. Copies of these references are attached to this Amendment.

[28] See Declaration by Strauss at ¶¶ 8-9; see also Declaration by Speroff at ¶¶ 8-9; see also Declaration by Westhoff at ¶¶ 8-9; see also Declaration by Coelingh Bennink at ¶¶ 3 and 5.

[29] See Holinka (1980), abstract, see also Declaration by Strauss at ¶¶ 15-16, 18 and 20; see also Declaration by Speroff at ¶¶ 15-16, 18 and 20; see also Declaration by Coelingh Bennink at ¶¶ 3 and 5.

[30] Declaration by Strauss at ¶ 16; Declaration by Speroff at ¶ 16; see also Declaration by Westhoff at ¶16; and Declaration by Coelingh Bennink at ¶¶ 5.

[31] Declaration by Strauss at ¶ 16; Declaration by Speroff at ¶ 16; see also Declaration by Westhoff at ¶16; and Declaration by Coelingh Bennink at ¶¶ 5.

very few practical applications exists, [32] and therefore teaches away from estetrol having any significant pharmacological effect.

Additionally, a person of ordinary skill in the art would have expected estetrol to be comparable to estriol.[33] Estetrol differs from estriol by only one hydroxyl group, and both estriol and estetrol are produced during pregnancy.[34] Hence, one of ordinary skill in the art would have believed that estetrol, like estriol, has a very short half-life on the order of minutes.[35]

Thus, the recited invention is patentable over the cited references because one of ordinary skill in the art would not reasonably expect that he or she could successfully use estetrol since it was believed that estetrol was not pharmacologically useful. When making a rejection under 35 U.S.C. § 103, the examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). As part of a *prima facie* case, an examiner must establish some reason to combine the references. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 131 (2007); *Takeda Chemical Industries, Ltd. v. Alpharpharm Pty., Ltd.*, 492 F.3d 1350, 1356-1357 (Fed. Cir. 2007). The *KSR* Court acknowledged the importance of identifying a reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. *KSR Int'l*, 127 S.Ct. at 1731; *Takeda Chemical*, 492 F.3d at 1356-1357. Repeatedly throughout the *KSR* decision, the Court discussed the importance that the result obtained by a particular combination was predictable to one of ordinary skill in the art. *KSR Int'l*, 127 S.Ct. at 1731 and 1739-1742.

A combination of known elements will not yield predictable results if the references teach away from the claimed invention. *Takeda Chemical*, 492 F.3d at 1359; *Ortho-McNeil Pharmaceutical, Inc. v. Mylan*, 520 F.3d 1358, 1364 (Fed. Cir. 2008); and *Ex parte Ikeda*, App. No. 08/352,079, Appeal 2008-0492, Slip Op. at 7 (BPAI Mar. 26, 2008). For example, in *Takeda Chemical*, the post-*KSR* Federal Circuit noted that the recited

[32] Declaration by Strauss at ¶¶ 15-16; Declaration by Speroff at ¶¶ 15-16; Holinka (1979); and Holinka (1980).

[33] Declaration by Strauss at ¶ 1; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[34] Declaration by Strauss at ¶ 1; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[35] Declaration by Strauss at ¶ 1; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

compound, which was a modified version of compound b, was not recognized at the pertinent time as a suitable candidate for treatment of Type II diabetes. 492 F.3d at 1359. *Takeda Chemical* involved United States Patent No. 4,687,777, which was directed to a compound for the treatment of Type II diabetes. *Id.* at 1352-1354. The defendant argued that the patent was obvious in view of a reference that disclosed compound b, because the claimed compound could be synthesized from compound b by routine means. *Id.* at 1357. However, the Federal Circuit affirmed that the patent was not obvious because the prior art taught away from choosing compound b as a starting point. *Id.* at 1359-1361. Compound b was known to have unwanted side effects, and there was nothing in the prior art to suggest that homologation would decrease the unwanted side effects. *Id.* at 1359-1360.

In a more recent case, the Board reversed an examiner's rejection for failing to provide the requisite reason to combine the references. *Ikeda*, App No. 08/352,079 at 7. The *Ikeda* application was directed to a method of removing hydrocarbons from exhaust gases. *Id.* at 2. In pertinent part, the claims recited an absorption catalyst B located downstream of a catalyst A in the direction of the exhaust gas. The claims were rejected as unpatentable under 35 U.S.C. § 103 in view of Swaroop, Abe and Patil. *Id.* at 3. Swaroop taught positioning the absorption catalyst B upstream of catalyst A. *Id.* at 5. To remedy the deficiency in the art, the examiner cited "Patil and Abe as evidence of the 'coventionality of positioning the adsorbent catalyst 1 either upstream or downstream of a [three-way] catalyst 3' and thus conclude[d] that it would have been obvious to one of ordinary skill in this art to select an appropriate location for the adsorbent catalyst 16 in the apparatus of Swaroop ...." *Id.* at 5-6. The Board held that

> The Examiner has failed to provide any cogent reason or technical discussion to support the conclusion that one of ordinary skill in this art would have employed the relative positions of the catalysts in Abe and Patil without the use of the other teachings of these references, namely an auxiliary heater and bypass lines with valving. Second, the Examiner has not explained why one of ordinary skill in this art would have used the teachings of Patil, requiring bypass lines and valving, when Swaroop specifically ***teaches away*** from the use of valving and bypass lines [*citation omitted*]. Third, the Examiner has not supplied convincing reasoning or technical discussion to support the proposed switch in relative position of the catalysts when Swaroop specifically teaches that the exhaust gas is "modified" by the adsorbent catalyst and this modified form of the exhaust gas is *then* sent to the main or three-way catalyst to undergo conversion to innocuous products [*citation omitted*]. ... Fourth,

> the Examiner has not explained why one of ordinary skill in this art would have ***proceeded contrary to the teachings of Patil***, namely the teachings that "it is not possible merely to place zeolite 'in-line' in the exhaust system with the [main] catalyst has reached an effective temperature and unconverted hydrocarbons would still be discharged to the atmosphere" [*citation omitted*].

Emphasis added, *Ikeda*, App. No. 08/352,079 at 7.

Following the reasoning stated in *Takeda Chemical* and *Ikeda*, the Office Action must provide some explanation why one of ordinary skill in the art would believe that estetrol would be pharmacologically useful when estetrol was believed to have too little estrogenic potency to be useful. As discussed above, prior to the publication of this invention, one of ordinary skill in the art would not expect estetrol to be pharmacologically useful because it was known that estetrol was a considerably weaker estrogen than the already weak estrogen estriol.

It was not until the Applicants discovered estetrol's very long terminal elimination half-life that it became apparent that estetrol could be pharmacologically useful. Prior to the disclosure of this invention, there was no publicly available data about the terminal elimination half-life of estetrol, about estetrol's binding to SHBG or about estetrol's effect on SHBG production.[36] Since estradiol and estriol have terminal elimination half-lifes of about 30 minutes and 5-10 minutes, respectively, it was believed that estetrol, another natural estrogen, would likewise have a short, if not shorter, terminal elimination half-life.[37] Unexpectedly, the Applicants discovered that estetrol has a terminal elimination half-life of about 28 hours.[38]

> A person of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only 1 hydroxy group and from estradiol by 2 hydroxy groups and (ii) both estriol and estetrol are produced during pregnancy. Hence, Applicants' finding that estetrol has a terminal elimination half-life that is 168-336 higher than that of the other pregnancy hormone estriol, was very unexpected and provided the clue towards its pharmacological usefulness.[39]

Like *Takeda Chemical*, one of ordinary skill in the art would have had no

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[36] Declaration by Coelingh Bennink at ¶¶ 4.

[37] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[38] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[39] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

reason to use estetrol because it was believed not to be pharmacologically useful. Maintaining a rejection based on the premise that estetrol can be used instead of estrone (E_1), estradiol (E_2) or estriol (E_3) is improper for the same reasons that the rejection in *Ikeda* was improper – because the prior art teaches away from using estetrol. As part of a *prima facie* case of obviousness, there must be some explanation why one of ordinary skill in the art would consider using estetrol when the prior art teaches that it is not pharmacologically useful. Since such an explanation has not been provided, a *prima facie* case of obviousness has not been established.

A. Response to Office Action of January 5, 2009

The Patent Office contends that "Kragie specifically teaches compositions containing estrogen function replacement (EFR) agents can replace the role of estrogens such as estradiol in the functions of human. ... Importantly, Kragie teaches that examples of EFR agents include a variety of estrogen compounds including estetrol (i.e. applicant's elected species."[40] The Patent Office acknowledges that Kragie teaches a variety of estrogen compounds. Thus, in order for the invention to be obvious, there must have been a reason to select estetrol over the other estrogen compounds. However, one would not have had a reasonable expectation that estetrol would be pharmacologically useful prior to the disclosure of this invention. Nor would one reasonably expected that estetrol could be used successfully in the method taught by Kragie. Prior to the disclosure of this invention, a person of ordinary skill would have been surprised to learn that estetrol was pharmacologically useful because, as previously established, estetrol had a very low receptor affinity,[41] and was expected to have a very short half-life.[42] Consequently, despite the fact that Kragie mentions estetrol as an example of an EFR agent, one of ordinary skill in the art would not have reasonably expected that he or she could successfully use estetrol in the method taught by Kragie since, in view on all the pharmacological data about estetrol that was available at the time, it was believed that estetrol was too weak and had a too short of a half-life to be pharmacologically useful.

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[40] Office Action at page 4.

[41] Declaration by Strauss at ¶¶ 15-16; Declaration by Speroff at ¶¶ 15-16; Holinka (1979); and Holinka (1980).

[42] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

Point II. It was unexpected to discover that estetrol was pharmacologically useful.

Additionally, the unexpected result that estetrol is pharmacologically useful because it has a long terminal elimination half-life rebuts the obviousness rejection. See *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1311, (Fed. Cir. 2006); see also *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). To establish unexpected results, the Applicant must "establish (1) that there actually is a difference between the results obtained through the claimed invention and those of the prior art, *In re Klosak*, 455 F.2d 1077, 59 CCPA 862 (1972); and (2) that the difference actually obtained would not have been expected by one skilled in the art at the time of invention, *Id.*; *In re D'Ancicco*, 439 F.2d 1244, 58 CCPA 1057 (1971)." *In re Freeman*, 474 F.2d 1318, 1324 (CCPA 1973). Without evidence to the contrary, an applicant need only provide substantially improved results and state that the results were unexpected. *Soni*, 54 F.3d at 750; *In re Lee*, App No. 10/091,061, 2007 WL 176690 at *3 (BPAI June 19, 2007).

In *Soni*, the examiner rejected certain claims as obvious in view of a combination of references. The applicant directed the examiner to the data in the specification, and argued that the increase in tensile strength and the increase in peel strength rebutted the rejections. *Soni*, 54 F.3d at 747. On appeal to the Federal Circuit, it was argued that the Board "could have taken judicial notice of the fact that higher molecular weight polymers would have been expected to tolerate higher filler loadings without degradation in properties and that it could have taken notice of the fact that it is the polymer *per se* that primarily determines the mechanical properties of a filled polymer composition." *Id.* at 750. However, the Federal Circuit found this argument fatally flawed because the Board failed to support its position with facts or evidence. *Id.* at 750; see also *Lee*, 2007 WL 176690 at *3. In summary, the Federal Circuit held that "[m]ere improvement in properties does not always suffice to show unexpected results. In our view, however, when an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results were *unexpected,* this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *Soni*, 54 F.3d at 751.

Estetrol has a terminal elimination half-life of 28 hours, which is 168-336 times greater than estriol's terminal half-life and about 56 times greater than estradiol's

terminal half-life.[43] Thus, there is an actual difference and substantial improvement between estetrol and estriol as well as between estetrol and estradiol.

One of ordinary skill in the art would have expected estetrol to be more comparable to estriol than estradiol given that (i) estetrol differs from estriol by only one hydroxyl group and from estradiol by two hydroxyl groups and (ii) both estriol and estetrol are produced during pregnancy.[44] Thus, one of ordinary skill in the art would have expected estetrol to have a terminal elimination half-life similar to estriol – on the order of a few minutes.[45] Unexpectedly, the Applicants discovered that estetrol's terminal elimination half-life was 28 hours.

The unexpectedly long terminal elimination half-life is associated with the unexpected pharmacological activity of estetrol. As discussed above, estetrol was known to be a very weak estrogen, so much so that it was dismissed by those of ordinary skill in the art as not being pharmacologically useful.[46] Thus, it was unexpected to discover that estetrol, due to its unexpectedly long terminal elimination half-life, would be pharmacologically useful.

Therefore, even assuming that a *prima facie* case of obviousness has been established, the unexpected results – that estetrol has an unexpectedly long terminal elimination half-life, and/or that estetrol is pharmacologically useful – provide evidence that the recited invention is patentable over the cited references.

A. Response to Office Action of January 5, 2009

Notwithstanding the arguments provided above – that one would not have reasonably expected estetrol to be pharmacologically useful – the inventors have unexpectedly established that (1) estetrol is pharmacologically useful for the recited method, and (2) that estetrol unexpectedly has such a long elimination half-life. The Patent Office

[43] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[44] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

[45] Declaration by Strauss at ¶ 18; Declaration by Speroff at ¶ 18; and Declaration by Westhoff at ¶18.

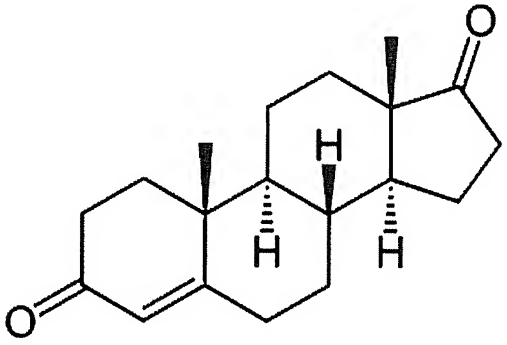
[46] Declaration by Coelingh Bennink at Exhibit B.

contends that one would have found it obvious to try estetrol to treat vaginal dryness.[47] However, the Applicants have established that one would not have reasonably expected estetrol to be useful. Thus, one would not have been motivated to try estetrol. For this additional reason, the Applicants respectfully request that this rejection be reconsidered and withdrawn because without some evidence showing that one would have expected estetrol to have the long elimination half-life, there would not have been a reason to try estetrol.

Point III. Claim 20 is patentable over Kragie, Willhite and Younglai.

Claim 20 has been rejected as unpatentable over Kragie, Willhite and Younglai;[48] or Sitruk-Ware, Spicer, Willhite and Younglai.[49] In these rejections, the Patent Office contends that Younglai teaches many precursors of estetrol, for example 15-2-hydroxyandrostenedione.

Androstenedione is represented by the following chemical structure:

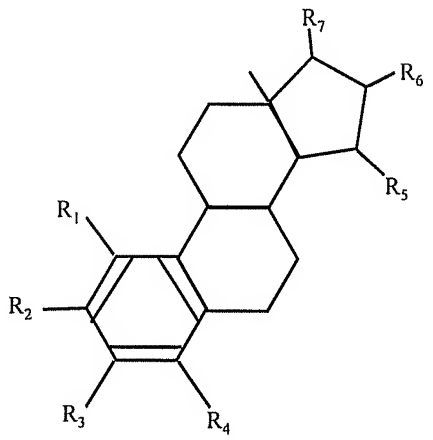


[47] Office Action at page 4.

[48] Office Action at pages 12-13.

[49] Office Action at pages 16-12.

Claim 20 requires that the precursors are derivatives of the estrogenic substances represented by the following formula:



in which formula R_1, R_2, R_3, R_4 independently are a hydrogen atom, a hydroxyl group or an alkoxy group with 1-5 carbon atoms; each of R_5, R_6, R_7 is a hydroxyl group; no more than 3 of R_1, R_2, R_3, R_4 are hydrogen atoms;

wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosydic residue containing 1-20 glycosidic units per residue.

Claim 20 *de facto* requires (i) that the ring carrying substituents R_1, R_2, R_3, R_4 comprises three unsaturated bonds and (ii) that R_6 and R_7 each independently represent a hydroxyl group or an O-acyl, wherein acyl is an acyl radical as defined above. Since neither dehydroandrostenedione nor 15-α-hydroxyandrostenedione meet these requirements, the combined teachings could Kragie, Willhite, and Younglai could not have lead a person of ordinary skill in the art to the subject matter of present claim 20.

CONCLUSION

Accordingly, Applicants respectfully request that the asserted rejections be reconsidered and withdrawn, and that claims 18-20, 24, 26, 28 and 32 be allowed.

Respectfully submitted,

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